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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
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| 10/020,472 | 10/30/2001 | Yung-Nien Chang | 397272000800 | 9279 |

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| EXAMINER | |
|---|---|
| WINKLER, ULRIKE | 4 |

| ART UNIT | PAPER NUMBER |
|---|---|
| 1648 | |

DATE MAILED: 03/26/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/020,472 | CHANG ET AL. | |
| | Examiner | Art Unit | |
| | Ulrike Winkler, Ph.D. | 1648 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☐ Responsive to communication(s) filed on _____ .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1-15* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-15* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *30 October 2001* is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

**Priority under 35 U.S.C. §§ 119 and 120**

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *5* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

## DETAILED ACTION

### *Information Disclosure Statement*

An initialed and dated copy of Applicant's IDS form 1449, Paper No 5 is attached to the instant Office Action.

### *Drawings*

The drawings are objected to, please see Notice of Draftsperson's Review attached to the instant Office Action. Figure 2 contains shading in the drawing showing the vector constructs. This makes the figure difficult to read because the writing is not legible. Correction is required.

Applicant is reminded of the new changes to the drawing requirements on the attached Notice of Draftsperson's Review. Applicant is required to submit the drawing corrections within the time period of response set in the instant office action (see 37 CFR 1.85(a)).

### *Claim Rejections - 35 USC § 102*

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-6, 11-13 and 15 are rejected under 35 U.S.C. 102(b) as being anticipated by Yu et al. (Journal of Virology 1996; IDS Paper No. 5).

The instant invention is drawn to a packaging cell line comprising three nucleic acid sequences in which each sequence has an effect on the next sequence, in a cascade like fashion.

The first product is a transactivator that is able to control the tetracycline-regulated promoter/operator (claim 3). The first or second nucleic acid comprises the tetracycline-regulated promoter/operator (claims 2 or 4). The second product is a Rev protein (claim 5). The third nucleic acid construct comprises a LTR promoter (claim 6). The viral gene product is a viral envelope or G protein (claims 7 and 10). The first product is a tat protein or chimeric protein comprising tat (claim 9). A cell line stably transfected with said nucleic acid constructs (claim 11). The cell line further comprises a conditionally replicating viral vector, derived from HIV having VSV G envelope, and growing the cell line under conditions that allow expression of the first product (claims 12-15).

> MPEP 2111.03 The transitional term "comprising", which is synonymous with "including," "containing," or "characterized by," is inclusive or open-ended and does not exclude additional, unrecited elements or method steps. See, e.g., *Genentech, Inc. v. Chiron Corp.*, 112 F.3d 495, 501, 42 USPQ2d 1608, 1613 (Fed. Cir. 1997) ("Comprising" is a term of art used in claim language which means that the named elements are essential, but other elements may be added and still form a construct within the scope of the claim.); *Moleculon Research Corp. v. CBS*, Inc., 793 F.2d 1261, 229 USPQ 805 (Fed. Cir. 1986); *In re Baxter*, 656 F.2d 679, 686, 210 USPQ 795, 803 (CCPA 1981); *Ex parte Davis*, 80 USPQ 448, 450 (Bd. App. 1948) ("comprising" leaves "the claim open for the inclusion of unspecified ingredients even in major amounts").

There is no limitation regarding the number of nucleic acids that are inserted into the cell, the cell can comprise more than just three nucleic acid constructs.

Yu et al. disclose a HIV packaging cell line. The cell line is transfected with a fusion protein consisting of a tetracycline repressor (tTA) and the activation domain of the herpes simplex virus VP16 domain (see page 4532, see figure 2 and results column 2). The gene of interest is controlled from the inducible promoter which consists of minimal CMV promoter coupled top the tetracycline operator sequences (see page 4533 column 1) the construct expresses Rev and Env. The Rev protein of the second nucleic acid is able to regulate the

expression of the late proteins from the viral sequences in the HXBΔP1Δenv. Here the removal of tetracycline would first induce the expression of Rev which in turn would induce Env, Gag, Pol and Vif expression. The cell line were tested using the HVP and HSN vectors and virus titer was assayed (see discussion page 4535, column 1 and figure 5). In the cell lines that have the additional vectors HVP or HSN, the order of the sequence (first, second an third product) changes, here the first viral construct is envelope expression vector with the teracyline operator, which activates expression of the HXBΔP1Δenv which provides Tat that will activate the HVP or HSN construct expressing viral genes. Therefore the instant invention is anticipated by Yu et al.

Claims 1, 3-8 and 10-15 are rejected under 35 U.S.C. 102(b) as being anticipated by Kafari et al. (Journal of Virology, 1999).

The instant invention is drawn to a packaging cell line comprising three nucleic acid sequences in which each sequence has an effect on the next sequence, in a cascade like fashion. The first product is a transactivator that is able to control the tetracycline-regulated promoter/operator (claim 3). The first or second nucleic acid comprises the tetracycline-regulated promoter/operator (claims 2 or 4). The second product is a rev protein (claim 5). The third nucleic acid construct comprises a LTR promoter (claim 6). The viral gene product is a viral envelope or G protein (claims 7 and 10). A cell line stably transfected with said nucleic acid constructs (claim 11). The cell line further comprises a conditionally replicating viral vector, derived from HIV having VSV G envelope, and growing the cell line under conditions that allow expression of the first product (claims 12-15).

Kafari et al. disclose a packaging cell line containing the tTA fusion product of the amino terminal-DNA binding domain of the tet repressor and the carboxyl-terminal activation domain of VP16 from herpes simplex virus. In the absence of tetracycline tTA binds to the *tet*-responsive element (TRE) in the *tet*-operator (*tet-O*) and efficiently activates transcription from downstream minimal promoters (see results page 577, column 2). To generate an inducible VSV-G pseudotyped lentivirus packaging cell line the VSV-G gene and HIV packaging cassette was cloned into a tetracycline inducible vector (pBIGFVG) (page 578, column 2). Both pPTK and pBIGFVG were cotransfected into SODkO cell line (page 579 column1). Since the activation of the HIV LTR in 293 cells is *tat* dependent, the induction of the pPTK packaging plasmid could be monitored by BFP expression. Expression of the pPTK will provide the *tat* protein, which in turn will activate the HIV LTR to transcribe and express BFP (page 579, column 2). Therefore, the instant invention is anticipated by Kafari et al.

***Claim Rejections - 35 USC § 103***

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out

the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-6, 9, 11-13 and 15 are rejected under 35 U.S.C. 103(a) as being unpatentable over Yu et al. (Journal of Virology 1996; IDS Paper No. 5) in view of Gosh et al. (Journal of Molecular Biology 1993).

The instant invention is drawn to a packaging cell line comprising three nucleic acid sequences in which each sequence has an effect on the next sequence, in a cascade like fashion. The first product is a transactivator that is able to control the tetracycline-regulated promoter/operator (claim 3). The first or second nucleic acid comprises the tetracycline-regulated promoter/operator (claims 2 or 4). The second product is a rev protein (claim 5). The third nucleic acid construct comprises a LTR promoter (claim 6). The viral gene product is a viral envelope or G protein (claims 7 and 10). The first product is a tat protein or chimeric protein comprising tat (claim 9). A cell line stably transfected with said nucleic acid constructs (claim 11). The cell line further comprises a conditionally replicating viral vector, derived from HIV having VSV G envelope, and growing the cell line under conditions that allow expression of the first product (claims 12-15).

Yu et al. teaches a HIV packaging cell line. The cell line is transfected with a fusion protein consisting of a tetracycline repressor (tTA) and the activation domain of the herpes simplex virus VP16 domain (see page 4532, see figure 2 and results column 2). The gene of interest is controlled from the inducible promoter which consists of minimal CMV promoter

coupled top the tetracycline operator sequences (see page 4533 column 1) the construct expresses Rev and Env. The Rev protein of the second nucleic acid is able to regulate the expression of the late proteins from the viral sequences in the HXBΔP1Δenv. Here the removal of tetracycline would first induce the expression of Rev which in turn would induce Env, Gag, Pol and Vif expression. The cell lines were tested using the HVP and HSN vectors and virus titer was assayed (see discussion page 4535, column 1 and figure 5). The instant invention does not teach a fusion protein comprising the (tTA) tetracycline repressor and the Tat activation domain.

Gosh et al. teach that Tat and VP16 are interchangeable in their ability to transactivate the HIV-1 LTR. The reference does not teach a packing cell line.

The reference Yu et al. and Gosh et al. are analogous art because they are from the same field of endeavor. It would have been obvious to one of ordinary skill in the art at the time the invention was made to replace the VP16 fusion protein construct taught by Yu et al with the Tat transactivator taught by Gosh et al.

> MPEP 2144.06 In order to rely on equivalence as a rationale supporting an obviousness rejection, the equivalency must be recognized in the prior art, and cannot be based on applicant's disclosure or the mere fact that the components at issue are functional or mechanical equivalents. *In re Ruff*, 256 F.2d 590, 118 USPQ 340 (CCPA 1958) *Smith v. Hayashi*, 209 USPQ 754 (Bd. of Pat. Inter. 1980) (The mere fact that phthalocyanine and selenium function as equivalent photoconductors in the claimed environment was not sufficient to establish that one would have been obvious over the other. However, there was evidence that both phthalocyanine and selenium were known photoconductors in the art of electrophotography. "This, in our view, presents strong evidence of obviousness in substituting one for the other in an electrophotographic environment as a photoconductor." 209 USPQ at 759.). An express suggestion to substitute one equivalent component or process for another is not necessary to render such substitution obvious. *In re Fout*, 675 F.2d 297, 213 USPQ 532 (CCPA 1982).

The inventions as a whole would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made. Therefore, the instant invention is obvious over Yu et al. in view of Gosh et al

Claims 1, 3-15 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kafari et al. (Journal of Virology, 1999; IDS Paper No. 5) in view of Gosh et al. (Journal of Molecular Biology 1993).

The instant invention is drawn to a packaging cell line comprising three nucleic acid sequences in which each sequence has an effect on the next sequence, in a cascade like fashion. The first product is a transactivator that is able to control the tetracycline-regulated promoter/operator (claim 3). The first or second nucleic acid comprises the tetracycline-regulated promoter/operator (claims 2 or 4). The second product is a rev protein (claim 5). The third nucleic acid construct comprises a LTR promoter (claim 6). The viral gene product is a viral envelope or G protein (claims 7 and 10). The first product is a tat protein or chimeric protein comprising tat (claim 9). A cell line stably transfected with said nucleic acid constructs (claim 11). The cell line further comprises a conditionally replicating viral vector, derived from HIV having VSV G envelope, and growing the cell line under conditions that allow expression of the first product (claims 12-15).

Kafari et al. disclose a packaging cell line containing the tTA fusion product of the amino terminal-DNA binding domain of the *tet* repressor and the carboxyl-terminal activation domain of VP16 from herpes simplex virus. In the absence of tetracycline tTA binds to the *tet*-responsive element (TRE) in the *tet*-operator (*tet-O*) and efficiently activates transcription from

downstream minimal promoters (see results page 577, column 2). To generate an inducible VSV-G pseudotyped lentivirus packaging cell line the VSV-G gene and HIV packaging cassette was cloned into a tetracycline inducible vector (pBIGFVG) (page 578, column 2). Both pPTK and pBIGFVG were cotransfected into SODkO cell line (page 579 column1). Since the activation of the HIV LTR in 293 cells is *tat* dependent, we could monitor the induction of the pPTK packaging plasmid by monitoring BFP expression. Expression of the pPTK will provide the *tat* protein, which in turn will activate the HIV LTR to transcribe and express BFP (page 579, column 2). The instant invention does not teach a fusion protein comprising the (tTA) tetracycline repressor and the Tat activation domain.

Gosh et al. teach that Tat and VP16 are interchangeable in their ability to transactivate the HIV-1 LTR. The reference does not teach a packing cell line.

The reference Kafari et al. and Gosh et al. are analogous art because they are from the same field of endeavor. It would have been obvious to one of ordinary skill in the art at the time the invention was made to replace the VP16 fusion protein construct taught by Yu et al with the Tat transactivator taught by Gosh et al.

> MPEP 2144.06 In order to rely on equivalence as a rationale supporting an obviousness rejection, the equivalency must be recognized in the prior art, and cannot be based on applicant's disclosure or the mere fact that the components at issue are functional or mechanical equivalents. *In re Ruff*, 256 F.2d 590, 118 USPQ 340 (CCPA 1958) *Smith v. Hayashi*, 209 USPQ 754 (Bd. of Pat. Inter. 1980) (The mere fact that phthalocyanine and selenium function as equivalent photoconductors in the claimed environment was not sufficient to establish that one would have been obvious over the other. However, there was evidence that both phthalocyanine and selenium were known photoconductors in the art of electrophotography. "This, in our view, presents strong evidence of obviousness in substituting one for the other in an electrophotographic environment as a photoconductor." 209 USPQ at 759.). An express suggestion to substitute one equivalent component or process for another is not necessary to render such substitution obvious. *In re Fout*, 675 F.2d 297, 213 USPQ 532 (CCPA 1982).

The inventions as a whole would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made. Therefore, the instant invention is obvious over Kafari et al. in view of Gosh et al

***Conclusion***

No claims allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ulrike Winkler, Ph.D. whose telephone number is 703-308-8294. The examiner can normally be reached M-F, 8:30 am - 5 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James Housel, can be reached at 703-308-4027.

The fax phone numbers for the organization where this application or proceeding is assigned are 703-308-4242 for informal communications use 703-308-4426.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

ULRIKE WINKLER, PHD.
PATENT EXAMINER 3/24/03